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Original Article

Bilateral Vestibular Hypofunction in a Tertiary Dizziness Center: Occurrence and Etiology

Eleonore Josephine Pröpper[1], Hanna Maria Koppelaar - van Eijsden[1], Tjard R. Schermer[1,2], Tjasse Bruintjes[1,3]

[1]Apeldoorn Dizziness Centre, Gelre Hospital, Apeldoorn, The Netherlands
[2]Department of Primary and Community Care, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands
[3]Department of Otorhinolaryngology, Leiden University Medical Centre, Leiden, The Netherlands

ORCID IDs of the authors: E.J.P. 0000-0003-4446-3384; H.M.K.v.E. 0000-0002-9805-0246; T.R.S. 0000-0002-1391-2995; T.B. 0000-0001-5955-8453.

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BACKGROUND: The primary goal of this study was to determine the occurrence of bilateral vestibular hypofunction in a specialized dizziness clinic and to assess the etiology in patients diagnosed with bilateral vestibular hypofunction. Secondary goal was to find out if the diagnosis was already made before the patient was seen at our clinic.

METHODS: A retrospective cohort study, including patients who visited our specialized dizziness center between January 1, 2008, and December 31, 2018, fulfilling the criteria for bilateral vestibular hypofunction according to the Classification Committee of the Bárány Society (2017). Data were collected regarding symptoms, causes, and vestibular function.

RESULTS: In total, 126 patients met our initial inclusion criteria, of which 103 patients met the Classification Committee of the Bárány Society criteria for bilateral vestibular hypofunction, so patients with bilateral vestibular hypofunction comprised 0.9% of the total population seen at our clinic. Mean age was 65.2 years and 49.5% were female. In only 29.1% of patients, the diagnosis was already made elsewhere. A definite cause was identified in 39.8%, the most common cause being ototoxicity.

CONCLUSION: About 1% of the patients visiting our dizziness clinic has bilateral vestibular hypofunction. In our patient population, ototoxicity was the most common cause of bilateral vestibular hypofunction, and in more than 40%, the cause remains unknown. In the majority of the cases, the diagnosis of bilateral vestibular hypofunction was first made at our clinic and not by the referring general practitioner or specialist. When using the Classification Committee of the Bárány Society criteria for bilateral vestibular hypofunction and presbyvestibulopathy, some patients with bilateral vestibular weakness and complaints cannot be categorized in either group.

KEYWORDS: Bilateral vestibulopathy, etiology, vestibular function tests

INTRODUCTION

Bilateral vestibular hypofunction (BVH) is a clinical condition defined by an absent or impaired function of the vestibular organs, the 8 cranial nerve, or a combination of both.[1] The clinical picture is characterized by oscillopsia—the experience that the environment is moving when the head is moving—and imbalance during motion. The imbalance is worse in poorly illuminated environments or when walking on uneven, spongy ground.[1-4] Bilateral vestibular hypofunction patients may also present with visual vertigo, cognitive deficits, impaired spatial orientation, and/or neurological, auditory, and/or autonomic symptoms.[3-5] The symptoms can be disabling, that is 41% of the patients perceive their handicap—measured with the Dizziness Handicap Inventory (DHI)—as moderate and 44% as severe.[6] Lucieer et al[7] found a mean DHI total score of 56.0 in BVH patients, indicating a moderate handicap. In the literature, prevalence rates for BVH vary from 28 to 81 per 100 000 people.[8-10] Hain[11] states that 1% of all the patients with dizziness visiting his clinic is diagnosed with BVH. Occurrence or prevalence rates of BVH in the Netherlands are currently lacking.

Several studies have shown that in 49%-80% of patients with BVH, a definite or probable cause can be identified, the most common causes being ototoxicity, bilateral Meniere's disease (MD), and meningitis (Table 1). Unfortunately, in 20%-51% of the patients,

Corresponding authors: Hanna Maria Koppelaar - van Eijsden, e-mail: h.van.eijsden@gelre.nl
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Table 1. Eetiology of Bilateral Vestibular Hypofunction[1,5,12,16]

Categories	Causes
Idiopathic	
Toxic	Aminoglycoside antibiotics, some chemotherapeutic agents, furosemide, aspirin, alcohol, vitamin-B12 deficiency, folate deficiency, hypothyroidism, styrene poisoning, combination of NSAID + penicillin
Infectious	Meningitis/encephalitis/cerebellitis, Borrelia, bilateral vestibular neuritis, Lues, Behçet, Herpes simplex virus
Autoimmune	Sarcoidosis, Cogan, Susac, Sjörgen, Wegener's, colitis, celiac disease, polyarteritis nodosa, antiphospholipid syndrome, other systemic diseases
Neurodegenerative	Superficial siderosis, CANVAS, multiple system atrophy, polyneuropathy, episodic ataxia, SCA3, SCA6, hereditary sensory and autonomic neuropathy type IV, other ataxias
Genetic	DFNA6, DFNA11, DFNA15, DFNB4, mutations on the 5q, 6q, 11q, or 22q chromosome and Muckle–Wells syndrome
Vascular	Vertebrobasilar dolichoectasia, supra- or infratentorial abnormality
Neoplastic	Neurofibromatosis type 2, bilateral vestibular Schwannoma, lymphatic metastasis, other malignant tumors
Trauma	Iatrogenic (e.g., bilateral cochlear implant), head trauma
Other ear pathology	Otosclerosis, cholesteatoma, or bilateral labyrinthitis
Congenital	CHARGE, Turner, Usher, Alport syndrome, enlarged vestibular aqueduct syndrome
Other	Vestibular atelectasis, presbyvestibulopathy, auditory neuropathy spectrum disorders

BVH, bilateral vestibular hypofunction; CANVAS, cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome; SCA, spinocerebellar ataxia; CHARGE, colomba, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, ear abnormalities and/or hearing loss DFNA, deafness autosomal dominant inherited hearing loss; DFNB, Deafness autosomal recessive hearing loss; NSAID, non-steroidal anti-inflammatory drug.

the cause remains unclear.[2,5,12] Multiple studies have focussed on this problem, and migraine and/or autoimmunity seem to play a role in the etiology.[12-15]

Due to the heterogeneous symptomatology of BVH and unfamiliarity with the condition among general practitioners (GPs), BVH is sometimes overlooked which may result in misdiagnosis or a diagnostic delay.[1,3,16] For years, it was the norm to diagnose BVH when the sum of the peak slow phase velocity (SPV) of all 4 irrigations was below 20°/s as measured by caloric testing.[4,17-20] However, no formal diagnostic criteria existed until 2017, when the Classification Committee of the Bárány Society (CCBS) published diagnostic criteria for BVH (see Table 2).[21] In addition, in 2019, the CCBS published diagnostic criteria for presbyvestibulopathy (PVP). Presbyvestibulopathy is defined as bilateral vestibular function loss due to aging. It presents with the same symptoms as BVH, but the criteria differ regarding age and outcomes of diagnostic testing (Table 2).[22] Therefore, PVP and BVH are considered as 2 separate disorders.

The primary goal of this study was to determine the occurrence of BVH in a specialized dizziness clinic and to assess the etiology in patients diagnosed with BVH. Secondary goal was to find out if the diagnosis was already made before the patient was seen at our clinic.

MATERIALS AND METHODS

Ethics

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments

Table 2. Diagnostic Criteria[21,22]

BVH	PVP
A. Chronic vestibular syndrome with the following symptoms: 1. Unsteadiness when walking or standing plus at least 2 or 3 2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements and/or 3. Worsening of unsteadiness in darkness and/or on uneven ground	A. Chronic vestibular syndrome (at least 3 months duration) with at least 2 of the following symptoms 1. Postural imbalance or unsteadiness 2. Gait disturbance 3. Chronic dizziness 4. Recurrent falls
B. No symptoms while sitting or laying down under static conditions	B. Age ≥ 60 years
C. Bilaterally reduced or absent VOR function documented by: 1. Bilateral pathological horizontal angular VOR gain < 0.6, measured by the video head impulse test or sclera-coil technique and/or 2. Reduced caloric response (sum of bithermal max. peak slow-phase velocity) on both side <6°/sec) and/or 3. Reduced horizontal angular VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair and a phase lead > 68° (time constant < 5 seconds)	C. Mild, bilateral peripheral vestibular hypofunction documented by at least 1 of the following: 1. VOR gain measured by video-HIT between 0.6 and 0.8 bilaterally 2. VOR gain between 0.1 and 0.3 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, Vmax = 50-60°/sec) 3. Reduced caloric response (sum of bithermal maximum peak SPV on each side between 6 and 25°/sec)
D. Not better accounted for by another disease	D. Not better accounted for by another disease

HIT, Head Impuls Test; VOR, vestibular–ocular reflex; SPV, slow-phase velocity.

up to 2013 and was approved by Gelre Hospitals Institutional Review Board (no: 2020-14).

Study Design
This study is a retrospective cohort study of all patients who experience imbalance symptoms and oscillopsia at the Apeldoorn Dizziness Centre—a tertiary referral center in a teaching hospital in the city of Apeldoorn, the Netherlands.

Patient Population
Patients were included in this study if they visited our clinic between January 1, 2008, and December 31, 2018, and met the criteria for BVH applicable at that time, that is (1) experienced imbalance during movement and/or oscillopsia and (2) had a reduced caloric response—summated mean peak SPV of 20°/s—and/or (3) a reduced gain during video head impulse testing (vHIT)—average gain of ≤0.6.

Patients were excluded if the outcomes of the vHIT or caloric testing were not available and/or if they had a unilateral vestibulopathy which was defined as a vestibular preponderance (VP) of 22% or higher.

After inclusion, we applied the CCBS criteria for BVH—as shown in Table 2—to our population and analyzed only those patients who met the new criteria for BVH.

Data Collection
Electronic patient files were reviewed and data were retrospectively collected regarding age, sex, date of the first medical consultation at our clinic, presenting symptoms, cause, and diagnostic test outcomes of BVH.

First, we collected the date on which the diagnosis of BVH was established in our clinic. If patients were seen multiple times in our clinic, the date of the first consultation at which the diagnosis of BVH was made was noted. Second, we determined from the information in the patient file if BVH was already diagnosed—based on vestibular function tests—elsewhere or suspected before visiting our clinic. Third, we determined if the referral was a second opinion or a primary referral from a GP.

Symptoms
Imbalance symptoms were defined as feeling dizzy, feeling lightheaded, and experiencing imbalance during motion. Oscillopsia was defined as blurry vision during motion and the experience of seeing multiple images during motion.

When the patient received one or more sessions of vestibular rehabilitation at our hospital, then in the context of usual care, the impact of dizziness on daily life was measured by the Dutch version of the DHI. Total DHI score pre-treatment was collected and categorized.[23,24] The DHI is a 25-item questionnaire to assess the impact of the dizziness on daily life in which each question can be answered with "No," "Sometimes," and "Always," graded respectively with 0, 2, and 4 points, total score ranges from 0 to 100.[25] Scores between 0 and 30 are considered to be mild, between 31 and 60 to be moderate, and between 61 and 100 to be severe.[26]

Cause of BVH
If possible, the underlying cause of BVH was derived from the information in the patient's medical file. Causes were classified on the basis of the categories described in Table 1. In case the cause of BVH was crystal clear, we classified it as "definite." When words like "probably," "in all probability," or "possible" were mentioned or a question mark was used, the cause was classified as "probable." In all other cases, we classified it as "idiopathic BVH."

Diagnostic Testing
Vestibular function was measured by means of the vHIT and bithermal caloric testing as previously described by van Esch et al.[27] For vHIT, we used the commercially available mono-ocular video oculography system of ICS Impulse, version 1.20 (OTOsuite Vestibular software: Otometrics, Taastrup, Denmark) . The VOR gain was defined as the ratio of the mean eye velocity (°/s) to the mean head velocity (°/s), and finally, the average gain was calculated.

For caloric testing, a conventional open-loop irrigation system in combination with a video-based system (Vestlab 7.0, Otometrics, Germany) was used to obtain and analyze the ocular responses. Data were collected regarding the maximum SPV of all 4 irrigations and the VP.

Statistics
IBM Statistical Package for the Social Sciences Statistics v.5 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were used to describe the patient characteristics.

RESULTS
During our study period, a total of 10 986 patients were seen at our clinic. In total, 126 patients met our initial inclusion criteria. When applying the CCBS criteria for BVH, a total of 103 patients were classified as having BVH (Figure 1). So, patients with BVH comprise 0.9% of the total patient population at our dizziness clinic.

Table 3 shows characteristics of our patient population. The mean age of the BVH patients was 65.2 ± 14.5 years (range, 25-89). Forty-six patients (44.7%) were diagnosed with BVH between the age of 51 and 70. Half of the BVH patients were female (49.5%). The mean average gain of the vHIT was 0.4 ± 0.2, and the mean maximum SPV was 7.4 ± 8.6. A total of 37 patients (35.9%) completed the DHI, of whom 16 rated their handicap due to dizziness to be moderate (43.3%).

In 43 of the 103 (41.7%) BVH patients, a cause could not be identified. A definite cause was identified in 41 (39.8%) of the patients, and a probable cause in 19 (18.5%) of the patients.

Idiopathic BVH is the largest category followed by ototoxicity (Figure 2). Twenty out of 29 patients in the toxic medication group had a history of gentamicin administration (19.4%). In 4 patients (3.9%), vancomycin, tobramycin, or other chemotherapeutic agents (e.g., cisplatin or carboplatin) were identified as the cause. A suspicion of toxic medication was present in 5 (4.9%) patients. After toxic medication (28.2%), the most frequent causes were meningitis (n = 5; 4.9%) and cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) (n = 5; 4.9%) (Figure 3).

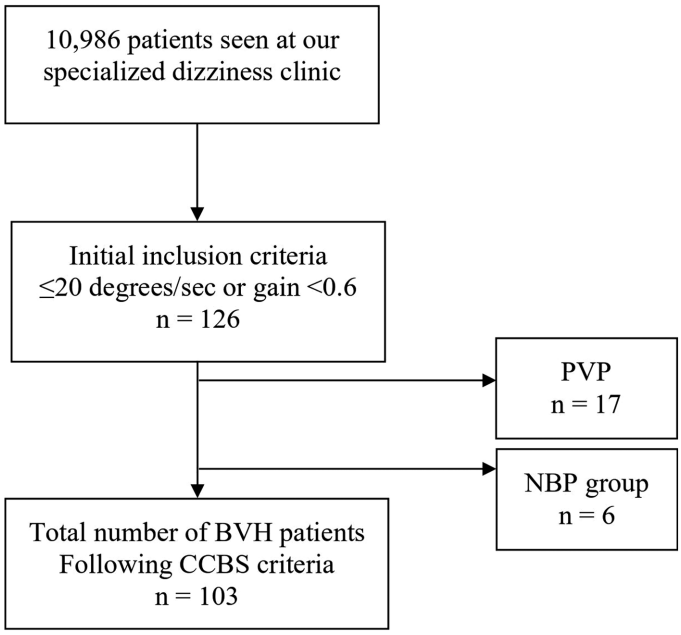

Figure 1. Flow diagram of inclusion of patients with bilateral vestibular hypofunction and distribution of diagnoses. n, number of patients; BVH, bilateral vestibular hypofunction; PVP, presbyvestibulopathy; NBP, not-BVH-or-PVP.

In 29.1% (n = 30), the diagnosis of BVH was confirmed in our clinic. A total of 22 patients were referred for a second opinion, of whom 7 patients had a suspicion of BVH. The remaining group of 39 patients was referred by their GP for diagnostic testing and treatment. In 11.7%, a referral letter was absent.

A total of 126 patients met our initial inclusion criteria, of whom 103 patients met the 2017 CCBS criteria for BVH. This comes down to a "misdiagnosis" of 23 patients. In hindsight, 17 of these patients (13.5%) could be diagnosed with PVP according to the 2019 diagnostic criteria for PVP. This leads up to 6 patients (4.8%) who neither met the diagnostic criteria for BVH nor for PVP ("Not-BVH-or-PVP"—NBP—group) (Figure 1). Patient characteristics, outcomes on vestibular functions tests, and DHI in the PVP and NBP subgroups are also shown in Table 3.

Table 3. Patients Characteristics

	Initial Group (n = 126)	BVH (n = 103)	PVP (n = 17)	NBP (n = 6)
Sex, n (%)				
Female	65 (51.6)	51 (49.5)	9 (52.9)	5 (83.3)
Male	61 (48.4)	52 (50.5)	8 (47.1)	1 (16.7)
Age				
Mean ± SD	64.7 ± 15.9	65.2 ± 14.5	73.0 ± 9.0	32.1 ± 16.1
Range	20-90	25-89	60-90	20-63
VmaxCO*				
n	103	80	17	6
Mean ± SD	9.3 ± 8.5	7.4 ± 8.6	16.8 ± 3.1	14.2 ± 1.9
Average gain vHIT**				
n	90	79	6	5
Mean ± SD	0.4 ± 0.2	0.4 ± 0.2	0.7 ± 0.1	0.8 ± 0.1
DHI***				
Mean ± SD	53.0 ± 21.5	53.5 ± 22.0	54.8 ± 18.1	26.0
DHI severity, n				
Mild	9	7	1	1
Moderate	18	16	2	
Severe	16	14	2	

BVH, bilateral vestibular hypofunction; DHI, Dizziness Handicap Inventory; NBP, no BVH or PVP; PVP, presbyvestibulopathy; SD, standard deviation; SPV, slow-phase velocity
*The summated peak SPV of all four irrigations measured by caloric testing
**The average score of the gain on both sides measured by vHIT
***Number of patients for whom a DHI score is available in the initial group n = 42, BVH group n = 37, PVP group n = 5, NBP group n = 1.

DISCUSSION

The aim of this study was to determine the occurrence and etiology of BVH in our specialized dizziness clinic. Secondary goal was to find out if the diagnosis was already established elsewhere. In summary, BVH was present in 103 patients, which comprises 0.9% of the total patient population of our dizziness clinic. The most common causes were idiopathic BVH, followed by ototoxic medication, meningitis, and CANVAS. In only 29.1%, BVH was diagnosed before the referral to our specialized dizziness clinic. Despite meeting our initial inclusion

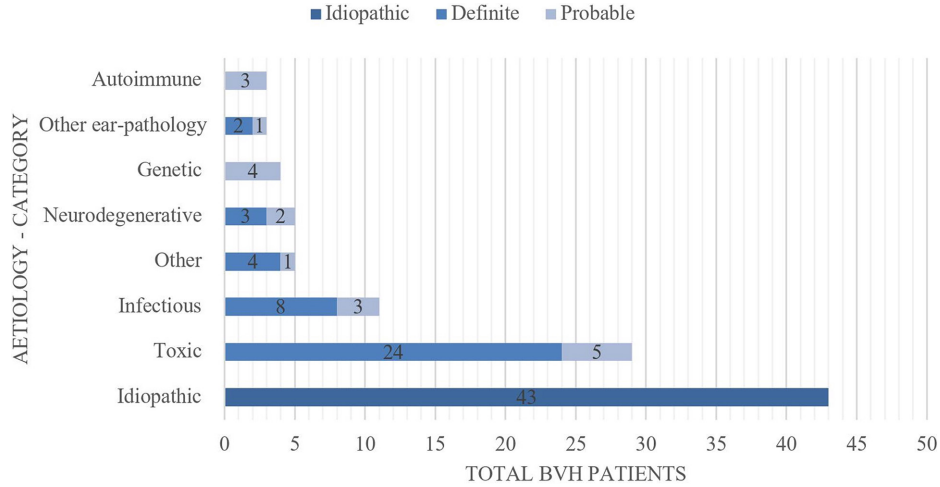

Figure 2. Distribution of etiology of bilateral vestibular hypofunction in main categories.[1] BVH, bilateral vestibular hypofunction. [1]Main categories are shown in Table 1.

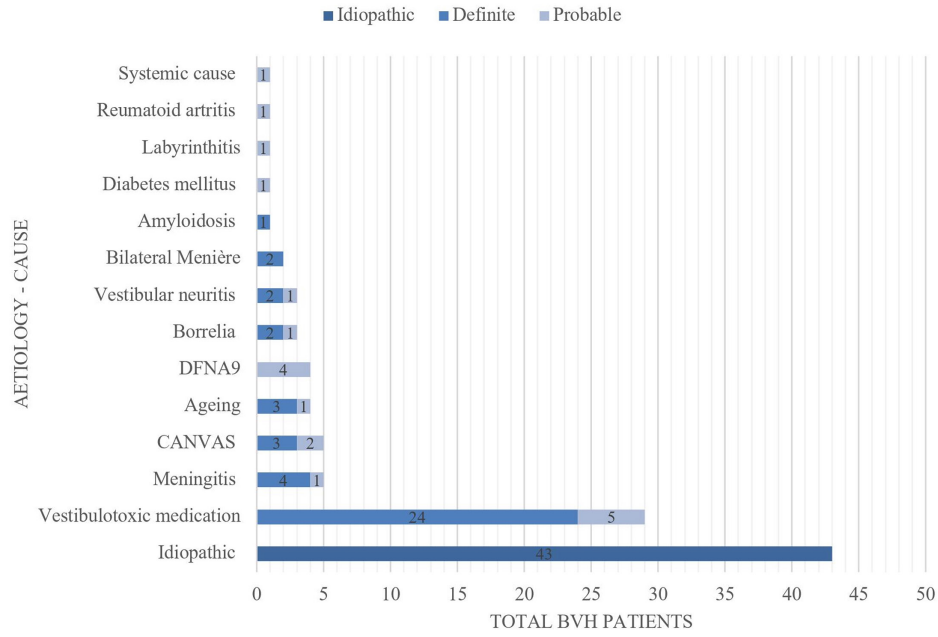

Figure 3. Distribution of etiology of bilateral vestibular hypofunction in causes.[1] DFNA9, deafness autosomal dominant-inherited hearing loss; CANVAS, cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome. [1]Causes are shown in Table 1.

criteria, 6 patients with complaints of imbalance and/or oscillopsia did not meet the newer CCBS criteria for BVH or PVP (the NBP group).

Hain[11] found that in his medical practice, which specializes in dizziness, about 1.0% of all dizziness is due to BVH. This is almost identical to the percentage of BVH patients in our clinic (0.9%). Occurrence rates of BVH specifically for the Netherlands are lacking. The study of Lucieer et al[12] conducted in the Netherlands is comparable to our study. They included 154 BVH patients in 2 years; however, it is unclear what the total population of patients was at their clinic; therefore, the occurrence rate could not be calculated.

The etiology of BVH was classified as idiopathic in 41.7% of the patients, a definite cause was identified in 39.8%, and a probable cause in 18.5%. These findings are largely in line with the findings in other studies.[2,5,12] The most common identified causes were ototoxic medication, meningitis, and CANVAS. Rinne et al[2] found a similar distribution; however, in their study, CANVAS was more frequent than meningitis. In the studies conducted by Lucieer et al[5] and Zingler et al[12], bilateral MD had a more prominent role in the list of most common causes. In our study, bilateral MD was identified in only 2 patients. Furthermore, compared to Lucieer et al[12], genetic causes were less common in our study.[12] Because our hospital does not have the opportunity to do genetic analysis, patients with a suspicion of the DFNA-9 mutation were referred to another (university) hospital, mostly by their GP. Feedbacks regarding these outcomes were not available and therefore classified as a probable cause. In 4 cases, we indicated aging as the cause of BVH.

Approximately one-third (35.9%) of the BVH patients had a certain diagnosis or suspicion of BVH when referred to our clinic. In two-thirds of the patients, a diagnosis of BVH was lacking, which illustrates the difficulty of diagnosing BVH and the need to refer to a tertiary center. As far as we know, so far no research has been done to assess if the diagnosis was already made before the patient was seen at a specialized dizziness clinic. Unfortunately, we did not collect data to specify the delay in diagnosis.

Our study shows the clinical consequences of the recently published diagnostic criteria for BVH and PVP. In total, 23 patients who were initially classified as having BVH did not meet the CCBS criteria for BVH. Seventeen patients could be classified as having PVP instead of BVH, and 6 patients (the NBP group) met the criteria for neither BVH nor PVP. The NBP group is a small group comprising relatively young, mostly female patients with weakness at caloric testing, and an average gain of 0.8 at vHIT. Dizziness Handicap Inventory scores in the PVP group are comparable to BVH group (54.8 vs. 53.5 points). This level of handicap is comparable to other studies where the average DHI score of patients with BVH varies from 46.9 to 62.0 points.[6,7,28,29] Inner hair cells of the vestibular organ do no regenerate; therefore, spontaneous recovery is unlikely,[30] and half of the BVH subtypes have a progressive nature, which means that the symptoms in the PVP and NBP group can progressively worsen over time.[16] This highlights the need of an adequate and early diagnosis and thereafter adequate information about the condition and its course and possible treatment options in all 3 groups.

In the CCBS consensus document with diagnostic criteria for BVH, a statement is made about the stringency of the criteria[21]: the new diagnostic criteria should be considered as "profound" BVH and less dramatic outcomes of vestibular function tests as "severe" BVH. In addition to this, the authors state that the summated maximum SPV of all 4 irrigations of 20°/sec or less is sensitive but not specific enough because of anatomical differences.[21] As a result, CCBS decided to use stricter diagnostic criteria regarding caloric testing. Starkov et al[31] (2021) published an update on diagnosing vestibular hypofunction.[31] They stated that there is still no worldwide consensus with respect to a standardized testing procedure and normative values for the vHIT and caloric testing. Values of both the vHIT and caloric testing depend to a great extent on the training and experience of

technicians, as well as the equipment used. Laboratories are therefore advised to determine specific normative values for their own setting; however, these values are often lacking. Therefore, in our opinion, the current CCBS criteria for BVH and PVP should be applied with this footnote in mind.

The strength of the current study is the long study period of 11 years and the rather large cohort size. Due to changing diagnostic criteria, we were able to show the clinical consequences of the new diagnostic criteria for BVH and PVP. The retrospective nature of the study is one of the limitations that may have influenced the results. The etiology was not determined in the same way in all the patients. For example, laboratory testing of blood samples was not done on every patient. As a consequence, the size of our idiopathic group could be overestimated. We encountered missing and incomplete data. Unfortunately, only a minority of the BVH patients had completed the DHI, and some patients had to be excluded due to missing results regarding vestibular function testing.

CONCLUSION

About 1% of the patients visiting our dizziness clinic has BVH. In our patient population, ototoxicity was the most common cause of BVH, and in more than 40%, the cause remains unknown. In the majority of the cases, the diagnosis of BVH was first made at our clinic and not by the referring GP or specialist. When using the CCBS criteria for BVH and PVP, some patients with bilateral vestibular weakness and complaints cannot be categorized in either group.

Ethics Committee Approval: Ethical committee approval was received from Gelre Hospitals Institutional Review Board (no: 2020-14).

Informed Consent: N/A.

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Declaration of Interests: The authors have no conflict of interest to declare.

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